INTRAVENOUS INJECTION OF TYPHOID VACCINE*

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A small series of cases of typhoid fever treated with intravenous injections of typhoid vaccine have been studied especially with respect to the changes in temperature, the leukocytes, the agglutinin and opsonin, the blood pressure, and the coagulation time. Observations were made several times each day. The vaccine used was a sterile suspension of typhoid bacilli heated at 60 C. for half an hour on 2 consecutive days, to which had been added 0.5% phenol.

CASE 1

The patient, a man 23 years of age, had been sick for 5 days with continuous fever; spleen palpable; pulse dicrotic; rose spots present. On the 15th day, the fever being still continuous, 20,000,000 typhoid bacilli were injected intravenously. Thirty minutes later the patient had a severe chill for 20 minutes; the temperature rose to 105.4, reaching its maximum 8 hours after the injection; in 10 hours it had fallen to 96. For the next 6 days fever of intermittent type ran between 100 and 102 and then the temperature fell to normal. The day after the injection the condition was much improved and convalescence set in with a rapid gain in weight and strength.

The leukocytes for 10 days preceding the injection of the vaccine averaged 5000 per cubic centimeter, 60% polymorphonuclears, 40% mononuclears. Four hours after the injection the count dropped from 4300 to 1500; in 18 hours it rose to 12000 and 24 hours later it fell to 5000, where it remained. At the initial drop the polymorphonuclears fell to 12% but increased rapidly, reaching 89% in 12 hours, and returning to the normal proportion in 36 hours.

The blood pressure fell from 120 to 105 after the injection and returned to 120 in 2 days.

The coagulation time showed no change during the reaction period (Boggs coagulometer). For agglutinin and opsonin see Chart 1.

CASE 2

The patient, a man 23 years of age, entered the hospital on the 5th day of illness, very sick and toxic; temperature 105, respirations 30, and leukocytes 4000. For the next 6 days his condition remained about the same. On the 11th day he had a moderate intestinal hemorrhage. On the 12th day 20,000,000 typhoid bacilli were injected. Twenty-five minutes later he had a severe chill for 20 minutes, with a rise in temperature from 103 to 105, rapid pulse and respiration, and a diffuse erythema. Three hours later a severe epistaxis, bleeding from the gums, and a small intestinal hemorrhage occurred, and

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morphin and horse serum were given. In 18 hours the temperature dropped to 96, pulse to 80, respiration to 20, and the general condition improved; there was a general eruption of rose spots. The following 9 days the temperature ranged from normal to 102.5. On the 22nd day 40,000,000 typhoid bacilli were injected. This was followed by a chill, rise in temperature to 105.4 and fall to normal in 12 hours. From this time on, the temperature remained normal and prompt convalescence took place.

For several days preceding the injection the leukocytes were approximately 4000, with 60% polymorphonuclears and 40% mononuclears. In 4 hours after the injection they fell to 1900, with a decrease in polymorphonuclears to 18%;

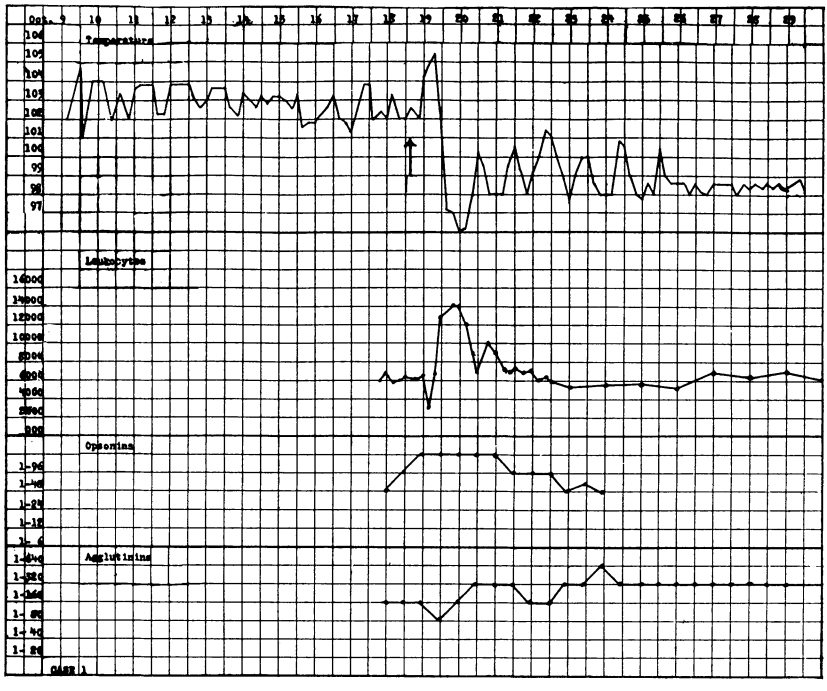

Chart 1.—Agglutinin, Opsonin, etc., Case 1.

in 12 hours the leukocytes increased to 16000, the polymorphonuclears to 88%; in 24 hours the count was 5000. Following the second injection the same initial drop occurred followed by a leukocytosis of 14800, polymorphonuclears 88%; in 36 hours the count was 5000.

For agglutinin and opsonin see Chart 2.

The blood pressure fell from 110 to 100 during the period of reaction and in 8 days gradually reached 130. At the second injection it fell to 120, returning to 130 the next day.

The coagulation time showed a slight increase during the chill from 3 minutes to 2 minutes.

CASE 3

A man, 27 years of age, entered the hospital on the 8th day with a fever of 100 to 103, palpable spleen, rose spots, and agglutinin in serum. On the 12th day of illness 20,000,000 bacilli were given intravenously; this was followed by only a slight chill, nausea and vomiting, and a rise in temperature from 101 to 103. The temperature continuing unchanged, on the 15th day a second injection of 40,000,000 was given. This was followed by a chill, rise in temperature to 100, succeeded by a drop in 12 hours to 97. The temperature then rose again and remained at from 99 to 102.4. On the 23rd day the patient was given a third injection of 80,000,000. This was followed by a severe chill and a rise in temperature to 106 with fall in 12 hours to 97.8, whereupon the temperature remained normal for 17 days. At this time the patient had a typical relapse which continued for a week.

Chart 2.—Agglutinin, Opsonin, etc., Case 2.

After each injection the blood pressure dropped from 124 to 98. After the first injection there was no fall in the number of leukocytes, but in 4 hours it rose to 11400 with a relative increase in the polymorphonuclears. The second and third injections produced a leukocytosis of 24000 for 36 hours without any initial drop. If an initial drop occurred in this case, it must have taken place earlier than the fourth hour, when the count was made.

For agglutinin and opsonin see Chart 3.

CASE 4

A woman, 30 years of age, entered the hospital on the 5th day of illness with all signs and symptoms of typhoid fever. Blood cultures were positive and typhoid bacilli were isolated from the stool and the urine.

On the 10th day the patient was given intravenously 40,000,000 bacilli; 20 minutes later she had a severe chill, which continued for 30 minutes, during which cyanosis developed; pulse 120; respiration 36. Eight hours later it rose again to 102.4 and assumed a remittent type. Otherwise the vaccine had little effect on the course, the temperature subsiding by lysis in 3 weeks.

The leukocytes, following the vaccine injection, dropped in 3 hours from 5000 to 2200, and then rose rapidly to 27000.

Agglutinin and opsonin determinations were not made.

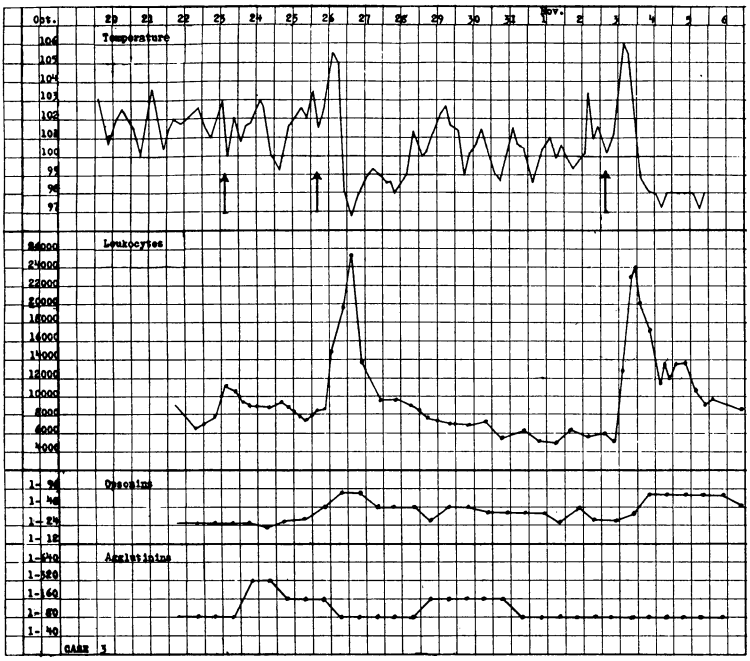

Chart 3.—Agglutinin, Opsonin, etc., Case 3.

The coagulation time, tests being made hourly beginning 2 hours before, and terminating 13 hours after, vaccine injection, fell from an average of 3 minutes to an average of 2 minutes during the reaction (Bogg's coagulometer).

CASE 5

A man, 21 years of age, entered the hospital about the 7th or 8th day of illness with a continuous temperature, leukocyte count 8000, positive blood culture and agglutinin test. The patient was very toxic and delirious. On the

12th day of illness he was given 40,000,000 typhoid bacilli. A chill followed and a rise in temperature to 106.6, succeeded by a fall in 88 hours to 97 and a return to between 102 and 105. The general condition was not improved and death took place on the 16th day. The blood pressure before the injection was 100; afterward it dropped to 78 and remained at this until death.

The leukocytes decreased slightly from 7000 and then rose in 12 hours to 19000 and increased gradually for 2 days to 22000 at the time of death.

(For agglutinin and opsonin see Chart 4.)

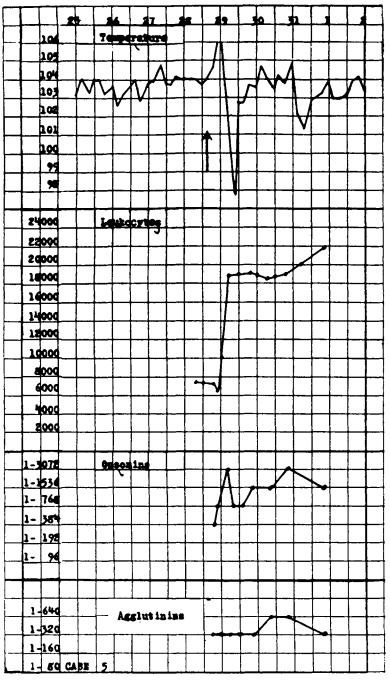

Chart 4.—Agglutinin, Opsonin, etc., Case 5.

CASE 6

A man, 20 years of age, entered the hospital on the 7th or 8th day of illness with a continuous fever, rose spots, palpable spleen, leukopenia, positive agglutination test and blood culture.

About the 13th day of illness 40,000,000 bacilli were given intravenously. This was followed by a typical reaction, but after the initial drop the temperature curve continued practically unchanged assuming a remittent type and falling by lysis. The condition generally, however, was distinctly improved.

The leukocytes made the characteristic drop, rose to 13000, in 10 hours fell to 7000, and then gradually to 5000.

For agglutinin and opsonin see Chart 5.

For purposes of comparison a perfectly normal man, 21 years old, was given 40,000,000 typhoid bacilli intravenously. In 30 minutes a severe chill

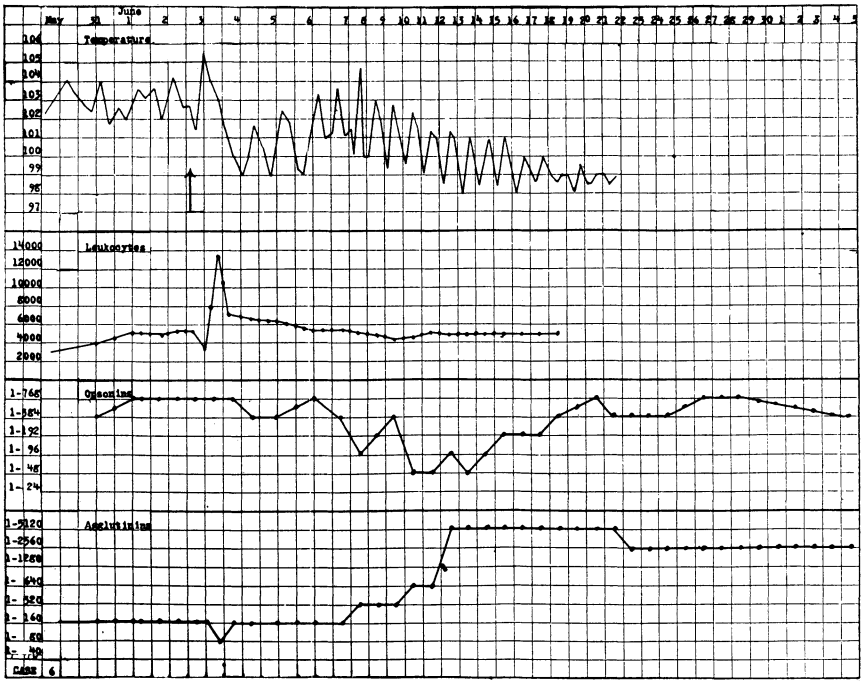

Chart 5.—Agglutinin, Opsonin, etc., Case 6.

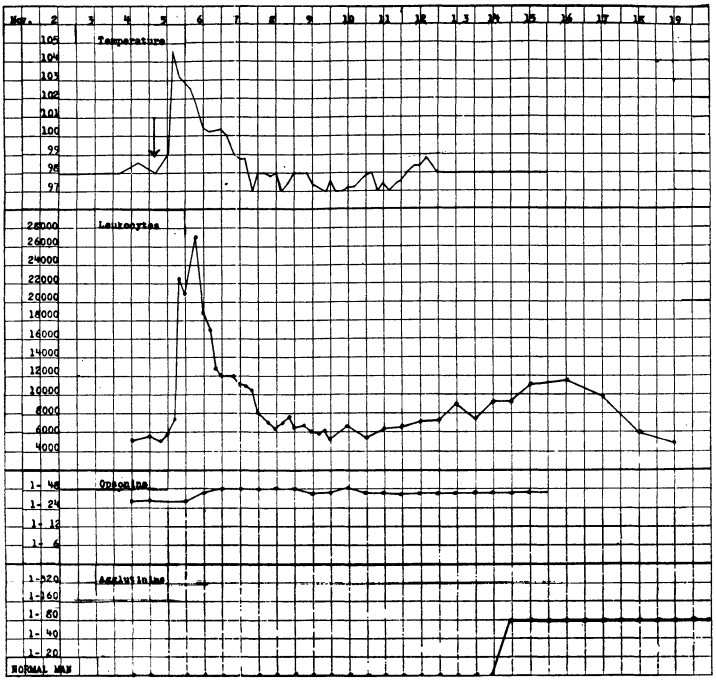

Chart 6.—Opsonin, Agglutinin, etc., Normal Man.

lasting 20 minutes came on, with a rise in temperature to 104.4 followed by gradual subsidence to normal in 48 hours. Seven days after the injection the spleen was just palpable and remained so for 5 days. On the 9th day after the injection the serum gave agglutination at 1:80 and remained at this titer for some time. The opsonin increased slightly the 2nd day (see Chart 6).

The leukocytes rose in 24 hours to 27000 and gradually declined in 3 days to 8000.

In all the cases the immediate effect of the vaccine was a chill for 20-30 minutes, followed by a rapid rise of temperature, which reached the maximum in 3-5 hours and then fell again in the course of the next 18 hours or so. The chill was accompanied by an increased rapidity of pulse and respiration and sometimes cyanosis. When the temperature fell, there was usually profuse perspiration.

In 1 case the temperature became remittent after 1 injection, in 2 cases after 2 or 3 injections; in 3 cases which received only 1 injection the fever continued, but changed from continuous to remittent, and here there was little or no effect on the course of the attack.

The leukocytes were counted every 4 hours just before, and after the injection of the vaccine. Before the injection the counts usually ranged from 4000 to 5000, polymorphonuclears 60% and mononuclears 40%; 4 hours or so after the injection the count usually was 1500 to 2000, polymorphonuclears 18-20% and mononuclears 78-80%; some 12 hours or so later the count usually had increased from 12000 to 20000, polymorphonuclears 80-88%.

The leukocytosis in the healthy man after injection of vaccine indicates that the leukocytosis in the typhoid patient after the injection of vaccine is not altogether specific as claimed by Gay and Chickering.[1] McWilliams[2] was unable to obtain any evidence of a specific hyperleukocytosis from typhoid vaccine in rabbits.

In determining the concentration of agglutinin and opsonin, we used the active serum in Cases 1, 2, and 3, and also in the case of the normal man, and in Cases 5 and 6, the heated serum. To determine the agglutinin extinction we used the macroscopic method, the tubes being incubated for 2 hours at 36 C. and read the following morning. To estimate the opsonin we used the extinction method, incubating the tubes for 7 minutes in the case of the active serum and for 25 minutes in the case of the heated serum. In 6 normal persons we found that the titer of the normal typhoid opsonin did not exceed 1-24. In most of our cases the titer of the agglutinin increased somewhat in 5-10 days

[1] Arch. Int. Med., 1916, 17, p. 303.
[2] Jour. Immunol., 1916, 1, p. 159.

after the injection, and the opsonin also increased, sometimes falling again, and there seemed to be no parallelism between the course of the agglutinin and the opsonin. The results of our observations on the concentration of the agglutinin and opsonin in the serum of typhoid patients injected intravenously with typhoid vaccine do not appear to lend any direct support to the view that the recovery or improvement observed in some cases is caused by a rapid increase in the formation of antibodies or rapid discharge into the blood of antibodies already produced.

As a rule, the blood pressure after the injection decreased 10-15 mm., gradually returning to the previous standard in a few days. The blood pressure was subnormal in all our cases and the least change resulted in those patients whose pressure was 100 or less.

Except in Case 4, only slight changes were observed in the coagulation time.

The results of the intravenous injection of the vaccine on the course of the disease in our cases may be summarized as follows:

One case was apparently aborted; 3 seemed distinctly improved and their course shortened; while 2 were unaffected, the patient in one of these dying.

SUMMARY

The immediate results of the intravenous injection of typhoid vaccine, such as chill, rise and fall of temperature, leukocytosis, and changes in the concentration of agglutinin and opsonin, usually in the direction of an increase, were the same in the normal man as in the typhoid patient, and our results do not support the view that the reaction is essentially specific. Except in so far as our results show that leukocytosis is rather constant after the injection of vaccine, they do not appear to support any particular view advanced to explain the action of intravenous injection of foreign protein in infectious diseases. The number of cases observed by us is too small to allow any conclusions as to the therapeutic effect of typhoid vaccine in typhoid fever, but the results obtained would seem to correspond fairly well with the results obtained in larger series.